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1/12/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	SINGH *et al.*	Atty. Dkt. No.:	RLL-263US
Serial No.:	10/616,240	Group Art Unit:	1614
Filing Date:	July 8, 2003	Examiner:	Unknown

Title: PROCESSES FOR THE APPLICATION OF ORAL DOSAGE FORMULATIONS OF MODAFINIL

Certificate of Mailing

I certify that this correspondence is being deposited with the United States Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 on January 9, 2004.

Kim Campbell

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMISSION OF PRIORITY DOCUMENT

Applicants transmit herewith a certified copy of Indian Patent Application No. 723/Del/2002 filed 8 July 2002 (08.07.2002) to which priority is claimed herein.

Respectfully submitted,

RANBAXY LABORATORIES LIMITED

By: _____
Jayadeep R. Deshmukh
Vice President - Intellectual Property

Dated: January 9, 2004

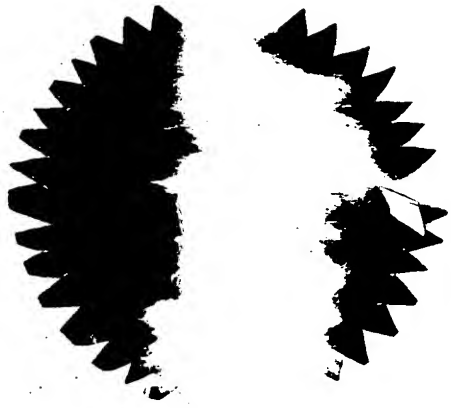
Ranbaxy Pharmaceuticals Inc.
600 College Road East, Suite 2100
Princeton, New Jersey 08540
Tel.: 609-720-5608
Fax: 609-514-9779

सत्यमेव जयते

INTELLECTUAL PROPERTY **INDIA**

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***723/Del/2002*** *dated* ***8th July 2002.***



Witness my hand this 22nd day of December2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

FORM 1

08 JUL 2002

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5 (2), 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR PREPARING MODAFINIL DOSAGE FORM FOR ORAL ADMINISTRATION"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. ROMI BARAT SINGH
b. PANANCHUKUNNATH MANOJ KUMAR
c. VISHNUBHOTLA NAGAPRASAD
d. SUNILENDU BHUSHAN ROY
e. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

DUPLICATE

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501 - 10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, ROMI BARAT SINGH, PANANCHUKUNNATH MANOJ KUMAR, VISHNUBHOTLA NAGAPRASAD, SUNILENDU BHUSHAN ROY, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. Romi Singh

(ROMI BARAT SINGH)

b.

(PANANCHUKUNNATH MANOJ KUMAR)

c.

(VISHNUBHOTLA NAGAPRASAD)

d.

(SUNILENDU BHUSHAN ROY)

e. Rajiv Malik

(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **682613** dated **17.06.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **8TH** day of **July, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

A PROCESS FOR PREPARING MODAFINIL DOSAGE FORM FOR ORAL ADMINISTRATION

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process of preparing modafinil dosage form for oral administration.

Modafinil is a wakefulness-promoting agent indicated for use in narcolepsy and idiopathic hypersomnia. The exact and precise mechanism of action is not fully revealed but it is thought to modulate the central postsynaptic alpha$_1$-adrenergic receptors. However, modafinil has a different pharmacokinetic profile compared to the sympathomimetic agents including amphetamines and methylphenidate.

The benzhydrylsulfinyl acetamide structure of modafinil makes it insoluble in water (<1mg/ml) and unstable at higher temperatures. Such physicochemical properties of the drug decrease its potential for abuse via injection and smoking leading to reduced cases of dependency compared to amphetamines.

Over the years, more than 40% of the potential candidates in drug discovery and research have failed to emerge as drugs due to their poor biopharmaceutic properties. Most of these are rejected due to poor solubility characteristics and further development is continued only if the new molecule has some marked advantage over the existing ones indicated for the similar use.

The most common approach to tackle such problem of insolubility is reduction of the drug particle size or micronization to a too small size of few microns, which increases the effective exposed surface area. Dosage forms containing micronized drug particles no doubt enhance solubility and consequently the bioavailability of such drugs but on the other hand it produces technical and economical problems. Highly micronized drug particles possess poor flow properties and high chances of re-agglomeration during processing. Re-agglomeration of micronized drug particles in some cases may be so problematic that the basic concept of enhancing the solubility by increasing the effective surface area may be lost.

The United States patent RE 37516 highlights this approach of size reduction and discloses a pharmaceutical composition comprising of at least about 95% of the modafinil particles having a diameter of less than about 200 µm.

In view of the prior art there is a dire need for a simple, cheaper and faster process of preparing modafinil dosage forms having desired dissolution rate. We have now discovered that problem of reagglomeration of micronized modafinil particles can be avoided by mixing coarse particles (diameter > 220µm) and fine particles (diameter < 220µm) in the ratio of 7:93 to 25:75 by weight. This combination of coarse and fine particles of drug improves the flow properties of the composition and thereby facilitates processing of dosage form. Further the problems of drug loss is also taken care along with better homogeneity. It also provides total drug release within 60-90 minutes.

Hence, the object of the present invention is to develop a process for the preparation of modafinil oral dosage form wherein about 7% - 25% by weight of modafinil particles have diameter > 220µm and about 93%- 75% by weight of modafinil particles have diameter < 220µm, and which dosage form releases at least 75% drug in about 45 minutes.

As used herein the term "coarse" means modafinil particles having diameter > 220 µm. The term "fines" means modafinil particles having diameter <220µm. Preferred mean particle size of fines is <180µm. Most preferred mean particle size of fines is <60µm. The ratio of coarse and fine particles may vary from a value of 7:93 to 25:75 by weight. Variation within this range does not affect the dissolution profile of modafinil dosage form. Preferred specific surface area of the total modafinil particles is at least 0.2 sq.m/gm.

The desired modafinil particle size may be obtained by conventional methods of milling and sieving. Methods of comminution of the modafinil particles may include air jet milling, multi-milling, ball milling or any other methods of particle attrition that produces size reduction.

These particles may be easily formulated into oral dosage formulations such as tablets, capsules by using the conventional excipients.

The excipients used may be selected from amongst diluents, binders, disintegrants, lubricants, glidants that are physiologically acceptable and compatible with modafinil and with other excipients of the formulation.

Diluents of the present invention may be selected from Lactose, mannitol, sucrose, microcrystalline cellulose, starch and calcium hydrogen phosphate.

Disintegrants may be selected from croscarmellose sodium, crospovidone and sodium starch glycolate.

Binders of the present invention may be selected from starch, sugars, gums and povidone.

Lubricants of the present invention may be selected from talc, magnesium stearate, calcium stearate, polyethylene glycol, hydrogenated vegetable oils, stearic acid, sodium lauryl sulphate, sodium stearyl fumarate and sodium benzoate.

Glidants may be selected from Colloidal silicon dioxide, aerosil, magnesium silicate or talc.

The tablets of the present invention may be prepared by mixing coarse and fine modafinil particles in geometric progression with filler(s) and disintegrant(s); wet granulating the blend with aqueous solution of binder; drying and sizing the granules; and compressing the granules.

Alternatively direct compression or dry granulation techniques may be used to prepare tablets, however wet granulation is preferred.

The tablets can be optionally coated using the standard coating processes.

The invention is further illustrated by the following examples but they should not be construed as limiting the scope of the invention anyway.

Example 1 and 2:

Formulation details for Modafinil Tablet

INGREDIENTS	Example #1 (mg/tablet)	Example #2 (mg/tablet)	Example #3 (mg/tablet)
Intragranular			
Modafinil (>220μ)	30	30	20
Modafinil (<220μ)	170 (d_{90}* 41 d_{50} 21)	170 (d_{90}* 23 d_{50} 12)	180 (d_{90}* 23 d_{50} 12)
Lactose	132	132	132
Starch	125	125	125
Croscarmellose Sodium	10	10	10
Povidone	10	10	10
Purified water	q.s.	q.s.	q.s.
Extragranular			
Croscarmellose sodium	10	10	10
Colloidal silicon dioxide	5	5	5
Talc	5	5	5
Magnesium stearate	2.5	2.5	2.5

*d_x y μm denotes x% of particles with diameter less than y μm

Process: Modafinil particles are mixed in geometric progression with starch, lactose and intragranular croscarmellose sodium. A water solution of povidone is prepared and used for granulating the above blend. The granules are dried at 60°C. The dried granules are sized and then mixed with extragranular croscarmellose sodium,

colloidal silicon dioxide, talc, and magnesium stearate and finally compressed into tablets.

Almost total drug release was attained in 60-90 minutes at 50 rpm using dissolution test apparatus USP II and water as the media wherein the drug has low solubility. The dissolution profiles of modafinil tablets prepared as per Examples 1 & 2 are given in Table-1.

Table-1: Dissolution data using USP Apparatus II, 900ml, 50rpm, water (values are indicated in cumulative percent release)

Time	Example #1 (%)	Example #2 (%)	Example #3 (%)
15 min	81	75	78
30 min	87	86	85
45 min	90	95	97
60 min	91	97	99
90 min	91	98	101

WE CLAIM:

1. A process for the preparation of modafinil oral dosage form wherein about 7% - 25% by weight of modafinil particles have diameter > 220µm and about 93%- 75% by weight of modafinil particles have diameter < 220µm, and which dosage form releases at least 75% drug in about 45 minutes.

2. The process according to claim 1 wherein about 7% by weight of modafinil particles have diameter > 220µm and about 93% by weight of modafinil particles have diameter < 220µm.

3. The process according to claim 1 wherein about 10% by weight of modafinil particles have diameter > 220µm and about 90% by weight of modafinil particles have diameter < 220µm.

4. The process according to claim 1 wherein about 15% by weight of modafinil particles have diameter > 220µm and about 85% by weight of modafinil particles have diameter < 220µm.

5. The process according to claim 1 wherein the specific surface area of the total modafinil particles is at least 0.2 sq.m/gm.

6. The process according to claim 1 wherein the dosage form is a tablet or capsule.

7. The process according to claim 6 wherein the dosage form is a tablet.

8. The process according to claim 7 wherein the tablet comprises other excipients in addition to modafinil.

9. The process according to claim 8 wherein the other excipients are selected from diluents, binders, disintegrants, lubricants and glidants.

10. The process according to claim 7 wherein the tablet is made by wet granulation.

11. The process according to claim 7 wherein the tablet is made by dry granulation.

12. The process according to claim 7 wherein the tablet is made by direct compression.

13. The process according to claim 7 wherein the tablet is coated.

14. The process according to claim 6 wherein the dosage form is a capsule.

15. A process for preparing modafinil dosage forms containing modafinil particles and other excipients substantially as described and illustrated by the examples herein.

Dated this **8TH** day of **July, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary